REMARKS

In paragraph 6, at pages 2 and 3 of the Office Action, the Examiner contend that the priority document (PP 3129) does contain support for differential methylation in liver cancer tissue DNA extracts.

Applicants respectfully submit that data demonstrating methylation of the GSTP1 gene in HepG2 liver cancer cells is presented in Fig. 4C, Panel C (note incorrectly described as Panel B) and described at page 22, lines 24-26 thereof. There is also reference at pages 10 and 21 to normal liver DNA that contains a limited amount of methylation near the transcription start site. Thus, Applicants respectfully submit that the priority document does support differential methylation in liver cancer. Hence, claims directed to liver cancer are entitled to a priority date of April 23, 1998.

In paragraph 8, on page 3 of the Office Action, the Examiner rejects Claims 1-14 and 17-34 under 35 U.S.C. §112, first paragraph.

Specifically, the Examiner objects to the expression "defined by (and inclusive of) sites 342-343 of SEQ ID NO:52 to CpG sites 581-582 of SEQ ID NO:54".

The present specification, at page 12, lines 15 to 18, indicates that the CpG sites are numbered relative to the transcription start site and that the nucleotide sequence numbering is according to the GST-Pi gene sequence of Genbank Accession No. M24485. The specification is hereby amended to include a sequence listing for the published sequence for GST-Pi, Genbank Accession No. M24485 (SEQ ID NO:60). Applicants

also provide herewith a new Sequence Listing including SEQ ID NO:60. For the Examiner's convenience, attached hereto is a chart showing the CpG sites in SEQ ID NO:60.

In view of the amendments to the claims to recite the nucleotides in SEQ ID NO:60 which define the CpG sites, Applicants respectfully submit that this aspect of the Examiner's rejection has been rendered moot.

The Examiner also objects to the expression "wherein the isolated DNA is not treated with a methylation sensitive restriction endonuclease prior to amplification in step (i)".

The Examiner will note that amended claim 1 does not include this expression, thereby rendering this objection moot.

Accordingly, Applicants respectfully submit that the claims meet the requirements of 35 U.S.C. § 112, first paragraph, and thus request withdrawal of the Examiner's rejection.

In paragraph 9, on page 6 of the Office Action, the Examiner rejects Claims 1-14 and 17-34 under 35 U.S.C. §112, second paragraph.

Specifically, the Examiner states that it is unclear what is meant by the expression "within the region of the GST-Pi gene and/or its flanking sequences defined by (and inclusive of) sites 342-343 of SEQ ID NO:52 to CpG sites 581-582 of SEQ ID NO:54". Further, the Examiner objects to expressions in the claims, such as "-43 to +53", as it is not clear how these numbers relate to any particular sequence in the specification.

In view of the amendments to the claims to recite the nucleotides in SEQ ID NO:60, which define the CpG sites,

Applicants respectfully submit that the Examiner's rejection has been rendered moot.

Further, on page 7 of the Office Action, the Examiner rejects Claims 1-14 and 17-34 in view of the recitation "prior to amplification in step (i)", because step (i) does not contain an amplification step.

As this recitation no longer appears in the amended claims, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

Before addressing the prior art rejections set out in paragraphs 11 to 13 of the Office Action, Applicants would like to draw the Examiner's attention to the amendments made to the claims.

Claim 1 and its dependent claims have been limited to an assay for prostate cancer. Moreover, Claim 1 has been amended to include the features of cancelled Claim 2. That is, Claim 1 includes a new step (ii) involving treating the isolated DNA of step (i) such that unmethylated cytosines are converted to uracil or another nucleotide capable of forming a base pair with adenine while methylated cytosines are unchanged or converted to a nucleotide capable of forming a base pairs with guanine. This treated DNA is then amplified according to step (iii). The target region for amplification is specified as comprising nucleotides 836-1117 of SEQ ID NO:60.

New Claim 77 is directed to an assay for prostate cancer wherein the target region for amplification comprises nucleotides 1232-1941 of SEQ ID NO: 60 (hereinafter referred to as the "transcribed region" or "intragenic region"). New Claims 78 to 91 depend either directly or indirectly from new Claim 77.

New Claims 92 and 109 are directed to an assay for liver cancer. New Claims 93 to 108 depend directly or indirectly from Claim 92.

Applicants now turn to the prior art rejections raised in the Office Action.

In paragraph 11, on page 7 of the Office Action, the Examiner rejects Claims 1-14 and 17-25 under 35 U.S.C. 103(a) as being unpatentable over Lee et al in view of Herman et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Lee teaches the use of PCR to amplify a GST-Pi promoter sequence fragment containing all 12 recognition sites for *HpaII*. 52 of 57 (91%) of the prostatic carcinoma DNA specimens demonstrated extensive somatic increases in deoxycytidine methylation, detected as amplification of target GST-Pi promoter sequences following *HpaII* digestion, but not following *MspI* digestion. Lack of methylation at any one of the 12 specified recognition sites did not result in amplification.

As indicated in the attached Declaration under 37 C.F.R. § 1.132 of Dr. Peter L. Molloy, this knowledge does not add further to the understanding of which CpG show differential methylation between cancer and normal tissue.

The Examiner's rejection appears to be based on an assumption that the presence of DNA methylation at one site in the promoter was known to be predictive of methylation at all other CpG sites (and similarly, that lack of methylation at one site is indicative of lack of methylation at all other sites). However, as indicated in the present application and supported by a number of additional references cited in Dr. Molloy's Declaration, it was clear that prior to the present invention this was not the case, and that levels of methylation at individual CpG sites within a promoter or CpG island could vary substantially. Thus, the extent of the sequence region and particular preferred or non-preferred sites that were suitable for development of assays of the type disclosed in Herman et al, were not known or predictable in the art. Moreover, even if it were accepted that the ordinary artisan were to apply the methylation specific PCR of Herman et al to the detection of methylated GST-Pi sequences in Lee et al, such application would be compromised by the lack of knowledge of which regions and specific CpG sites provide clear discrimination between cancer and normal tissue DNA (see paragraph 16 of Dr. Molloy's Declaration).

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Lee et al alone or in combination with Herman et al, and thus request withdrawal of the Examiner's rejection.

Furthermore, with regard to Claim 77, the claim specifies that the target region is within the transcribed region, i.e., CpG sites +1 to +55, of the GST-Pi gene. As indicated in Dr. Molloy's Declaration, there is no teaching or suggestion in the cited

references of an assay based on the transcribed region of the GST-Pi, as claimed in new Claim 77. In fact, use of CpG sites within the transcribed region of the GST-Pi gene was contra-indicated (see paragraphs 23-25 of Dr. Molloy's Declaration).

Additionally, Lee et al and Herman et al are silent in relation to liver cancer, and therefore do not render Claims 92 and 109 obvious.

In paragraph 12, on page 14 of the Office Action, the Examiner rejects Claims 26-29 under 35 U.S.C. §103(a) as being unpatentable over Lee et al in view of Herman et al and in further in view of Jhaveri et al and Morrow et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, the combination of Lee et al and Herman et al does not teach or suggest the present invention. Further, for the following reasons, Jhaveri et al and Morrow et al do not provide the deficiencies which exist in Lee et al and Herman et al.

The Examiner concedes that neither Lee et al nor Herman et al teach specific primers for the amplification of the "CpG island" of GST-Pi. Applicants respectfully submit that neither Jahveri et al nor Morrow et al provide any further information that identifies what regions or CpG sites are differentially methylated between cancer DNA and DNA from normal tissues that is needed for development of assays of the type described by Herman et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Lee et al alone or in combination with Herman et al, Jhaveri et al and Morrow et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 13, on page 16 of the Office Action, the Examiner rejects Claims 30-34 under 35 U.S.C. 103(a) as being unpatentable over Lee et al in view of Herman et al and in further view of Tchou et al.

Specifically, the Examiner contends that data in support of claims to detection of liver cancer was introduced in filing of the complete specification, and was not present in the original Provisional Application.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, the combination of Lee et al and Herman et al does not teach or suggest the present invention. Further, for the following reasons, Tchou et al does not provide the deficiencies which exist in Lee et al and Herman et al.

As noted above and in Dr. Molly's Declaration, data demonstrating methylation of the GST-Pi gene in HepG2 liver cancer cells has been presented in Fig 4C, Panel C (note, incorrectly described as Panel B in the priority application), and described at page 22, lines 24-26 thereof. There is also reference at pages 10 and 21 to normal liver DNA that contains a limited amount of methylation near the transcription start site. Thus, as the date of filing of the Provisional Application precedes the

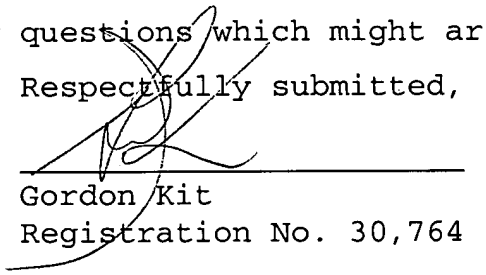
publication date of Tchou et al, Applicants respectfully submit that Tchou et al is not prior art.

Accordingly, Applicants respectfully request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner s invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,



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Date: January 3, 2005